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RESEARCH ARTICLE

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The exercise in pulmonary arterial hypertension (ExPAH) study: A randomized controlled pilot of exercise training and multidisciplinary rehabilitation in pulmonary arterial hypertension

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Abstract

Pulmonary hypertension (PH) is characterized by progressive dyspnea, fatigue, and reduced exercise capacity. Despite medical treatment, outcomes remain poor. While exercise training is well established in patients with heart failure, it is less established in patients with PH. This single-blind, randomized controlled pilot study examined the feasibility and effect of 12-week outpatient exercise (multidisciplinary rehabilitation or home walking program) on hemodynamics using cardiac magnetic resonance imaging (cMRI) and right heart catheterization (RHC) in patients with pulmonary arterial hypertension (PAH), a subset of PH. Sixteen participants were randomized to either multidisciplinary outpatient rehabilitation or a home walking program for 12 weeks. Primary outcome measures were changes in right ventricular ejection fraction and stroke volume index on cMRI. Secondary outcome measures included hemodynamics on RHC, quality of life (QOL), muscle strength (handgrip and vital capacity) and 6-min walk test. This preliminary, pilot study suggests that outpatient exercise interventions may be associated with improved hemodynamic function (mean pulmonary artery wedge pressure, stroke volume, and stroke volume index), QOL (PH symptoms, depression, and anxiety), and muscular strength (vital capacity and handgrip strength) for people with PAH, but was not adequately powered to make any formal conclusions. However, our outpatient programs were feasible, safe, and acceptable to participants. Future studies are required to further explore the potential hemodynamic benefits of exercise in PAH.

KEYWORDS
exercise, pulmonary hypertension, rehabilitation

INTRODUCTION

Pulmonary hypertension (PH) is characterized by progressive dyspnea, fatigue, and reduced exercise capacity. If untreated, PH may result in right ventricular (RV) failure and death.[1] Historically, exercise was not recommended in patients with PH due to concerns regarding excessive RV strain.[2] However, exercise has been shown to be safe and is associated with improvements in endurance and quality of life (QOL) in patients with pulmonary arterial hypertension (PAH), a subset of PH.[3–6]

Many exercise training (ET) studies[7–9] have utilized a 3-week inpatient/12-week home rehabilitation protocol. This 15-week high dosage protocol involving exercise for a minimum of 5 days/week (aerobic, strength, and respiratory muscle training for 3 weeks, then a home program of exercise >5 days/week, with a combination of aerobic and strength training).[7] improved exercise capacity, QOL, and hemodynamics.[10] Despite a lower exercise dosage, several small outpatient studies have also reported improvements in exercise capacity and QOL.[11–15] However, no outpatient exercise studies to date have measured hemodynamic changes using a right heart catheter (RHC) or cardiac magnetic resonance imaging (cMRI), the gold standard for hemodynamic measures.

In Australia, inpatient rehabilitation for PAH is not widely available. As access to PAH-specific inpatient rehabilitation programs is limited, an 8-to 12-week outpatient program is a more practical alternative.[16] However, it remains unknown whether programs of this format and intensity are beneficial for patients with PAH. This study sought to determine whether the "real world" frequency of ET and/or multidisciplinary rehabilitation (MDR), that is, 1 h, twice weekly, for 12 weeks, was feasible and acceptable to PAH patients. This study also sought to explore whether outpatient ET/MDR programs have a beneficial effect on hemodynamics and RV structure.

METHODS

This was a pilot single-blind, randomized controlled trial across two sites: a major quaternary metropolitan hospital (St Vincent's Hospital, Sydney) and a smaller, regional center (Coffs Harbour Pulmonary Arterial Hypertension Clinic), both in New South Wales, Australia. Participants were consecutively recruited over 4 years (2016–2019) from PAH outpatient clinics at these sites and randomized to either outpatient MDR or home ET via a 1:1 group allocation as previously described[17] (Figure 1). The study was undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement[18] (Figure 2). Ethics approval was obtained from St Vincent's Hospital Human Research Ethics Committee (HREC/14/SVH/340). The study was registered with the Australian and New Zealand Clinical Trials Registry, trial reference ACTRN12615001041549.

Recruitment criteria were as follows: adults >18 years, with PAH, diagnosed by RHC at any time before screening, with mean pulmonary artery pressure (mPAP) ≥25 mmHg and resting pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. Participants were World Health Organization (WHO) functional Class I–III with stable PAH-specific medications in the 3 months before enrolment, as published previously.[17]

The study interventions lasted 12 weeks.[17] The intervention group (MDR) attended twice-weekly 1-h exercise sessions, supervised by a physiotherapist, which involved 20 min aerobic work (Borg rating of perceived intensity [RPE] 12–13), 20 min light weights (starting at 1 kg), and 10 min respiratory muscle training using a Phillips inspiratory muscle trainer. The MDR group also had three semistructured individual telepsychology sessions with a psychologist.[17] The control group (ET) received written instructions to increase self-directed walking up to 30 min/day, 5 days/week. The study comprised a 12-week intervention period, and a subsequent 12-week observational period (see Figure 1). There were no exercise sessions or instructions to continue to exercise after the 12-week intervention period.

Since the two study interventions and our primary outcome measure (cMRI) were novel, feasibility and patient acceptability were key outcomes. Feasibility was assessed by recording the number of eligible participants declining study enrolment; adherence with the intended study protocol for enrolled participants; and a brief satisfaction questionnaire rating participant experience on Likert scales (see Supporting Information Document) after Week 12. Primary outcome measures were RV ejection fraction (RVEF) and stroke volume (SV) measurements by cMRI; secondary outcomes were as previously described,[17] as in Table 1. Cardiac MRI (collected at baseline and 12 week) were analyzed by a single-blinded cardiologist, at the end of the study.

Statistical analysis

Descriptive statistics were used to summarise study cohort baseline demographics. Mixed factorial repeated-measures analyses of variance (RM-ANOVAs) examined longitudinal outcome data over time, using a within-subject factor of TIME (baseline, Week 12; then from Weeks 12–26 to assess if any changes were sustained) and a between-subject factor

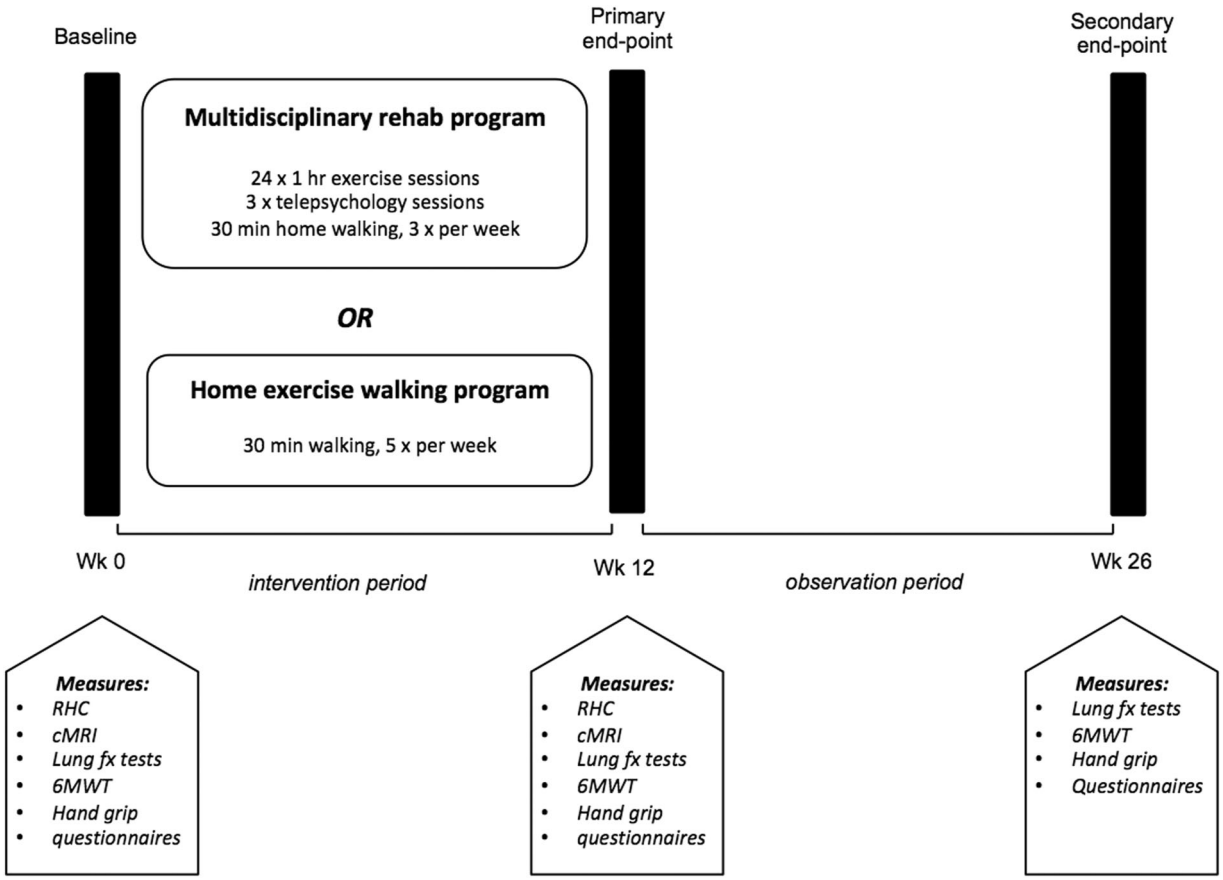

FIGURE 1 Trial assessment schedule. Schematic representation of trial interventions and assessment schedule. A 12-week intervention period was followed by a 12-week observational period. All participants completed outcome assessments at baseline, Week 12 and Week 26. Participants were allocated to either MDR or ET—a home walking program. ET, exercise training; fx, function; MDR, multidisciplinary rehabilitation

of GROUP (intervention, control). A separate ANOVA was computed to examine the main effect of time, and the interaction between group and time for each outcome variable. Raw statistical and p values are reported, with significance considered at the traditional threshold of $p < 0.05$ (two-tailed). To account for multiple comparisons made in this exploratory study, significance was also considered after secondary false discovery rate (FDR) correction, according to the Benjamini and Hochberg method.[19] All statistical analyses were conducted using SPSS software (version 26, IBM).

RESULTS

Participant enrolment

A total of 73 patients with PAH were screened (Figure 2). Forty-six patients were eligible (63%). Sixteen participants consented and were randomized as previously described[6]; nine participants to control (ET) and seven participants to intervention (MDR). The mean age of enrolled participants was 54. The cohort was predominantly Caucasian and female (Table 2). Participants were on average 7.9 ± 4.9 years from the time of PAH diagnosis at study enrolment (Table 2). Twenty-seven patients were ineligible (Table 3).

Acceptability and feasability

Recruitment rates were low. Only 35% of eligible patients screened consented to participate (16/46). The main reason for declining was insufficient time to participate (37%). Some did not provide an explicit reason for declining; however informal feedback from participants indicated the study tests required (notably the invasive RHC) may have been too onerous. Given the slow recruitment ($n = 16$ over 4 years; and no recruitment possible due to coronavirus restrictions for 2020 and 2021), a decision was made to terminate the study and undertake a preliminary analysis.

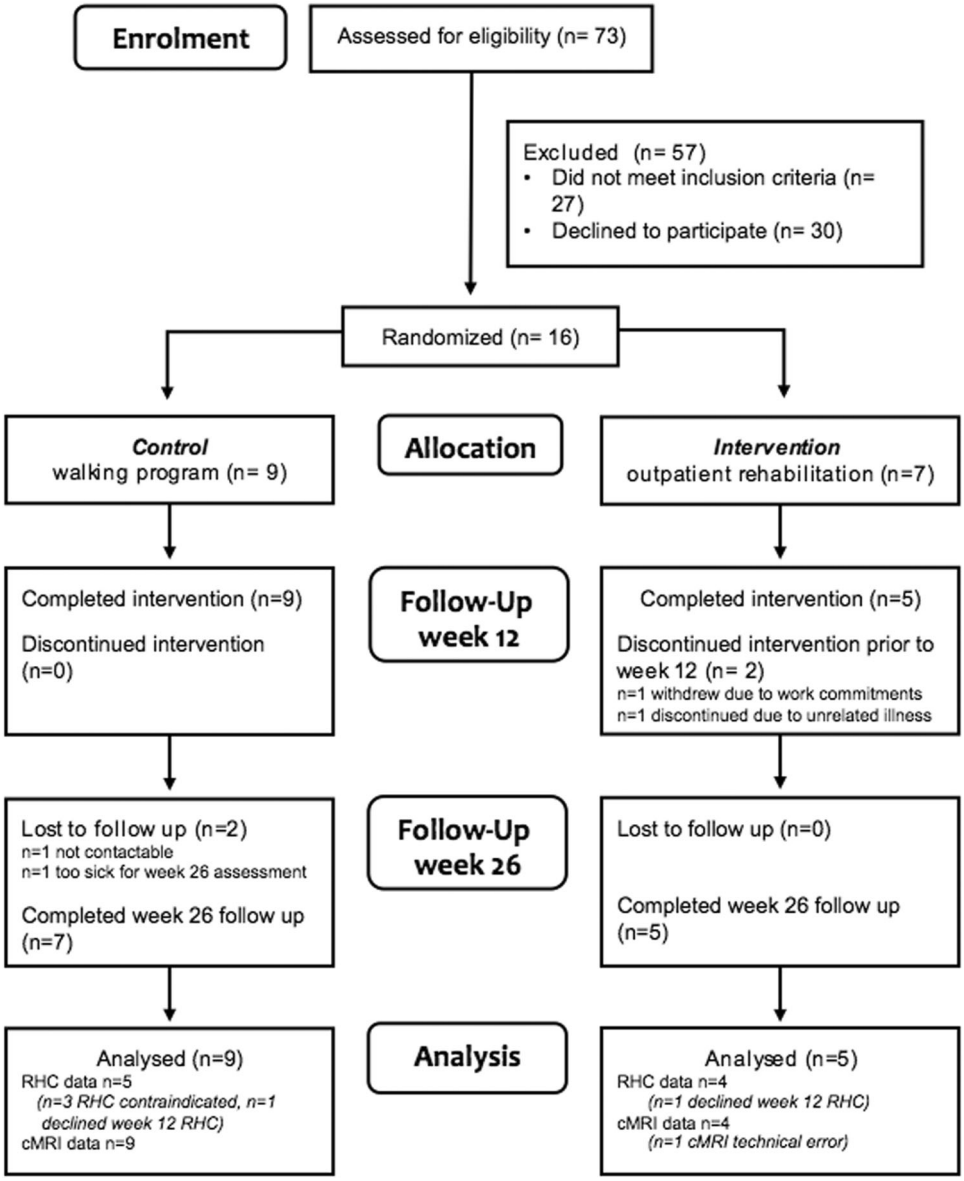

FIGURE 2 Allocation and CONSORT diagram

Study participants found the ET and MDR programs acceptable and enjoyable. Overall, 86% (12/14) of participants reported they found the interventions "very helpful/extremely helpful," and 93% (13/14) reported they were "enjoyable."

Investigators and study therapists found both programs feasible to deliver. However, a number of study protocol deviations occurred. These included: two participants declining an RHC at Week 12 (due to time commitments); three participants having no RHCs performed during the study due to medical contraindications (low platelets, previous adverse event, medical instability); and one participant being too unwell to undertake Week 26 assessments (Figure 2). Two participants in the ET group were lost to follow-up (Figure 2).

ADHERENCE

Adherence in the MDR group was generally high, however, two participants in the intervention group exited the study before Week 12 (time constraints, and unrelated medical illness). Session attendance for the remaining participants was excellent, with the remaining four out of five participants attending all 24 sessions. All participants achieved a training effect by working at Borg RPE of 12–13 (self-rated moderate intensity) during supervised sessions.

In the ET group, home diary documentation demonstrated high levels of adherence, with seven of the nine walking program participants completing a home exercise diary (92% adherence; mean of 55/60

TABLE 1 Outcome measures

Primary outcome measures
Change from baseline to Week 12 in
• Right ventricular ejection fraction • Stroke volume and stroke volume index
Secondary outcome measures
Change from baseline to Week 12 in
• RHC parameters: RAP, mPAP, mPAWP, CO, CI • cMRI: LVEDVI, RVEDVI, CO, CI • QOL: CAMPHOR and DASS-21 • Functional outcome measures: Lawton's IADL • Exercise capacity (6MWT) • Muscle strength (VC, % predicted VC and DHGS)
Change from Week 12 to Week 26 in
• QOL: CAMPHOR and DASS-21 • Functional outcome measures: Lawton's IADL • Exercise capacity (6MWT) • Muscle strength (DHGS)

Abbreviations: 6MWT, 6-min walk test; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CO, cardiac output; DASS-21, depression and anxiety stress scale 21; DHGS, dominant hand grip strength; IADL, instrumental activities of daily living; LVEDVI, left ventricular end diastolic volume index; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; QOL, quality of life; RAP, right atrial pressure; RHC, right heart catheterization; RVEDVI, right ventricular end-diastolic volume index; VC, vital capacity.

recommended walking sessions completed at home). Two ET participants did not document any home exercise due to poor literacy. A review of home diaries for remaining participants found that all increased activity levels to recommended guidelines (walking at least 5 days a week, for 30 min/day). The average distance walked increased from 2.2 km in the first three sessions to 2.51 km in the last three sessions (for those who recorded distance).

CLINICAL OUTCOMES

There were no serious adverse events. Three mild adverse events occurred (rash from chlorhexidine used for the RHC; transient muscle ache and one episode of syncope in the context of concurrent lower respiratory tract infection). Nil injuries were sustained, and nil hospitalization was required.

No significant group-by-time interaction was observed for any primary or secondary outcome measure at Week 12 compared to baseline, for MDR/ET groups. Main effects from baseline to Week 12 across the entire cohort were then considered. Significant changes were observed for a number of outcomes, including improvements in mPAWP, SV, SVI, VC, CAMPHOR, DASS-21 depression and anxiety scales and handgrip strength, when considered individually (Table 4) but not when FDR correction was applied because the trial was underpowered (see also Supporting Information: Table A.1). When FDR correction was applied across all outcomes, no main effects retained statistical significance at the adjusted threshold. There were no significant changes noted on any outcome measures between Week 12 (immediately postintervention), and follow-up at Week 26 (Supporting Information: Table A.2).

DISCUSSION

We found that 12-week outpatient ET/MDR programs were feasible, safe, and beneficial for patients with PAH. While not powered to detect significant effects, this exploratory study suggested improvements from baseline to Week 12 across several outcomes, including hemodynamics (mPAWP, SV, SVI), frailty (handgrip strength), and QOL outcomes (symptoms of PAH, depression, and anxiety). These findings suggest that MDR/ET may be associated with both physiological and psychological benefits for people with PAH, and further research should focus on outcomes identified as potential markers of improvement, including mPAWP, SVI, and handgrip strength.

In our cohort, cMRI demonstrated a trend to improvement in SV and SVI from baseline to Week 12. As previously noted,[20] SV reflects RV function and is the best prognostic hemodynamic measure in PH.[20] The minimally important difference (MID) for SV in patients with PH is between 8 and 12 ml.[20] We found a mean increase in SV of 8.2 ml for the MDT group, and 4.7 ml for the ET group, suggesting a possible clinically significant improvement for the MDT group; though this requires confirmation in larger studies. To our knowledge, this study is the first to demonstrate the potential for improvement in RV function with outpatient exercise in PAH patients. If confirmed, this adds further weight in support of outpatient exercise-based rehabilitation in the management of PH.

Ehlken's landmark study[10] is the only study that has demonstrated an improvement in hemodynamic measures by RHC (mPAP, PVR, CO, and CI) following a targeted nonpharmacological intervention in patients with PH. We did not find similar improvements in these parameters with our interventions. This was likely impacted by our small sample size, but may also be related to exercise dosage; our protocol included less therapy (total of 24 h for MDT group and 30 h for the ET

TABLE 2 Participant baseline demographics

Variable	Control (ET), $n = 9$	Intervention (MDR), $n = 7$	All participants, $n = 16$
Age (years, standard deviation)	55 ± 15.8	52.9 ± 15.3	54 ± 15.1
Gender, *n* (%)			
Female	7 (78)	6 (86)	13 (81)
Male	2 (22)	1 (14)	3 (19)
Weight (kg, SD)	78.9 ± 15.4	71 ± 15.6	75.4 ± 15.6
Body surface area (m^2)	1.9 (0.2)	1.8 (0.2)	1.8 (0.2)
Ethnicity,*n* (%)			
Caucasian	9 (100)	4 (57)	13 (81)
South-East Asian	0 (0)	1 (14)	1 (6)
Indian	0 (0)	1 (14)	1 (6)
Arabic	0 (0)	1 (14)	1 (6)
Highest level of education, *n* (%)			
Primary school	2 (22)	0 (0)	2 (13)
High school	4 (44)	0 (0)	4 (25)
Technical and further education	1 (11)	4 (57)	5 (31)
University	2 (22)	3 (43)	5 (31)
Type of PAH, *n* (%)			
Idiopathic	3 (33)	6 (86)	9 (56)
Connective tissue-associated PAH	3 (33)	0 (0)	3 (19)
Congenital heart disease-associated PAH	2 (22)	0 (0)	2 (13)
Portal hypertension-associated PAH	1 (11)	1 (14)	2 (13)
Number of PAH-specific medications, *n* (%)			
Monotherapy	1 (11)	1 (14)	2 (13)
Dual therapy	4 (44)	5 (71)	9 (56)
Triple therapy	4 (44)	1 (14)	5 (31)
Class of PAH-specific medication, *n* (%)			
ERA	8 (89)	6 (86)	14 (88)
PD5E inhibitor	8 (89)	5 (71)	13 (81)
sGC stimulator	1 (11)	1 (11)	2 (13)
Prostacyclins	4 (44)	1 (17)	5 (31)
Anticoagulation, *n* (%)			
Nil	5 (56)	3 (33)	8 (50)
Warfarin	3 (33)	3 (33)	6 (38)

Variable	Control (ET), $n = 9$	Intervention (MDR), $n = 7$	All participants, $n = 16$
Direct oral anticoagulant	1 (11)	1 (14)	2 (12)
WHO functional class, *n* (%)			
I	0 (0)	1 (14)	1 (6)
II	6 (66)	6 (86)	12 (75)
III	3 (33)	0 (0)	3 (19)
IV	0 (0)	0 (0)	0 (0)
Mean 6MWT (m, SD)	421 ± 137	499 ± 95	455 ± 123

Abbreviations: 6MWT, 6-min walk test; ERA, endothelin receptor antagonist; ET, exercise training; MDR, multidisciplinary rehabilitation; PAH, pulmonary arterial hypertension; PD5E inhibitor, phosphodiesterase-5E inhibitor; sGC, soluble guanylate cyclase.

TABLE 3 Characteristics of ineligible patients

Reason for ineligibility ($n = 27$)	Number (%)
Functional Class IV	10 (37)
Enrolled in another PAH-specific trial	5 (19)
Medical comorbidities	5 (19)
PAH-specific medication change in the preceding 12 weeks	2 (7)
Already enrolled in a formal exercise program	1 (4)

Abbreviation: PAH, pulmonary arterial hypertension.

group), compared to over 220 h of exercise per patient for Ehlken's cohort.[10] Our cohort also differed in that we did not include patients with chronic thromboembolic associated pulmonary hypertension.

Despite the lower intensity and therapy dose of our outpatient programs, some encouraging improvements in hemodynamics as measured by RHC were noted. In our cohort, mPAWP demonstrated some improvement after the interventions, suggestive of an improvement in left-sided cardiac function. It is well documented that exercise improves LVEF in patients with heart failure with reduced ejection fraction (HF-rEF).[21] The reduction in mPAWP may also be due to ventricular interdependence, possibly suggesting improvement of the RV. To our knowledge, this is the first study to demonstrate the potential for reduced mPAWP in patients with PAH following a nonpharmacologic intervention.

Our study interventions were found to be feasible and well-accepted by participants. However, a notable proportion of those screened was ineligible (Table 3), or declined to participate (Figure 2). This suggests that whilst participants may enjoy and benefit from MDR/ET, likely uptake among the wider PH population is less certain. We have previously identified multiple barriers to exercise in patients with PH,[22] such as fear and uncertainty regarding the appropriateness of exercise. Unless these barriers are addressed, the wide uptake of exercise interventions such as those trialed here for PH patients will likely be poor. Furthermore, in this study many potential (and included) participants were reluctant to undergo invasive investigations such as RHC for study purposes. Future studies could consider using less invasive cMRI outcome measures (namely SVI and RVEF) as alternative primary outcomes, to optimize recruitment.

Overall, our trial interventions were found to be safe, with no observed serious adverse events. Noting that one syncopal episode occurred during self-directed walking in the context of a concurrent respiratory tract infection, we advise future exercise interventions for people with PAH temporarily cease during any intercurrent illness.

In line with previous studies, we saw improvements in a number of quality-of-life domains following our interventions.[7–10] These included improvements in PAH-related symptoms (such as fatigue, breathlessness and mood), anxiety and depression, as noted in other cardiac rehabilitation studies.[23,24] Greater exercise capacity likely contributed to these improvements in QOL, which may in turn increase confidence and independence in usual daily activities.[25]

VC also appeared to improve from pre- to postintervention, which may reflect some improvement in respiratory muscle function. Although the ET intervention did not include specific respiratory muscle training (unlike the MDR intervention, which did utilize

TABLE 4 Change in clinical outcomes from baseline to Week 12

Outcome	Intervention (MDR)		Control (ET)		Total/pooled cohort		Main effect of time (RM-ANOVA)
	Baseline ($n = 7$) Mean (95% CI)	Week 12 ($n = 5$) Mean (95% CI)	Baseline ($n = 9$) Mean (95% CI)	Week 12 ($n = 9$) Mean (95% CI)	Baseline ($n = 14$) Mean (95% CI)	Week 12 ($n = 14$) Mean (95% CI)	F (df), p Value
RHC mPAP (mmHg)	35 (25.3–45.7)	35 (20.9–49.0)	36.2 (27.1–45.3)	32 (19.5–44.5)	35.9 (29.0–42.7)	33.5 (24.1–42.9)	2 (1,7), $p = 0.198$
RHC mPAWP (mmHg)	12.5 (9.9–15.1)	10.8 (7.5–14)	13.2 (10.9–15.6)	9.8 (6.9–12.7)	**12.9 (11.1–14.6)**	**10.3 (8.1–12.4)**	**10.3 (1,7), $p = 0.015$***
RHC PVR (WU)	5.4 (2.6–8.2)	5.1 (2.3–8)	4 (1.6–6.5)	4 (1.5–6.5)	4.7 (2.9–6.6)	4.5 (2.6–6.4)	0.515 (1,7), $p = 0.496$
cMRI SV (ml)	86.8 (61.4–112.1)	95 (68.6–121.30	81.3 (64.5–98.2)	86 (68.4–103.6)	**84.0 (68.8–99.3)**	**90.5 (74.7–106.3)**	**6.7 (1,11), $p = 0.025$***
cMRI SVI (ml/m^2)	50.6 (35.6–65.6)	55.4 (40.2–70.1)	43.6 (33.6–53.6)	46.2 (36–56)	**47.1 (38.1–56.1)**	**50.8 (41.7–59.9)**	**8 (1,11), $p = 0.016$***
cMRI RVEF (%)	56.5 (40.1–72.9)	59 (41.4–76.6)	47.3 (36.4–58.3)	49.6 (37.8–61.3)	51.9 (42.0–61.8)	54.3 (43.7–64.8)	4.2 (1,11), $p = 0.064$
cMRI CO (L/min)	4.4 (3.0–5.9)	4.7 (3.1–6.3)	4.8 (3.8–5.8)	5 (3.9–6.1)	4.6 (3.7–5.5)	4.8 (3.9–5.8)	0.51 (1,10), $p = 0.493$
cMRI CI (L/min/m^2)	2.5 (1.9–3.2)	2.6 (1.9–3.4)	2.6 (2.1–3.0)	2.7 (2.2–3.2)	2.6 (2.2–2.9)	2.7 (2.2–3.1)	0.59 (1,10), $p = 0.459$
VC (% predicted)	93 (73.1–112.9)	96 (77.2–114.8)	77.9 (62.1–93.7)	81.3 (66.4–96.1)	**85.4 (72.7–98.1)**	**88.6 (76.6–100.6)**	**4.8 (1,11), $p = 0.05$***
CAMPHOR symptoms (0–25)	4.4 (−3.1–9.1)	2.2 (-2.2–6.6)	9.8 (6.3–13.3)	6.4 (3.2–9.7)	**7.1 (4.2–10.0)**	**4.3 (1.6–7.1)**	**12.46 (1,12), $p = 0.04$***
DASS-21 depression (0–21)	3.6 (-2.7 to 9.9)	1.4 (-2.2 to 5.0)	6.8 (2.1–11.5)	2.4 (-.22 to 5.1)	**5.2 (1.3–9.1)**	**1.9 (-0.3–4.2)**	**9.11 (1,12), $p = 0.011$***
DASS-21 anxiety (0–21)	1.4 (-3.6 to 6.4)	0.2 (-3.6 to 3.9)	6.3 (2.6–10.1)	4.3 (1.6–7.1)	**3.9 (0.8–6.9)**	**2.3 (−0.1 to 4.6)**	**5.1 (1,12), $p = 0.043$***
6MWT (m)	527 (413–640)	544 (421–667)	421 (337–505)	438 (347–530)	473.8 (403.2–544.4)	491.1 (414.3–567.8)	3.4 (1,12), $p = 0.09$
DHGS (kg)	27.4 (20–34.8)	29.1 (21–37.2)	26.1 (20.6–31.6)	27.1 (21.1–33.2)	**26.8 (22.1–31.4)**	**28.1 (23.1–33.2)**	**5.88 (1,12), $p = 0.032$***

Note: Results for key clinical measures from repeated measures analyses of variance (RM-ANOVA), examining the effect of time on outcomes from baseline to Week 12; further results can be seen in Supporting Information: Table A.1. Data are presented as mean (95% confidence interval) for the intervention and control groups (white). Mean values for the cohort as a whole are indicated in gray, accompanied by the main effect F statistic, degrees of freedom, and p values.

Abbreviations: 6MWT, 6-min walk test; CI, cardiac index measured by cMRI; cMRI, cardiac magnetic resonance imaging; CO, cardiac output measured by cMRI; DASS, depression and anxiety stress scale 21; DHGS, dominant handgrip strength; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheter; RVEF, right ventricular ejection fraction; SV, stroke volume; SVI, stroke volume index

*Raw $p \leq 0.05$; also noted in bold. No significant group-by-time interactions were observed.

inspiratory muscle training), VC still appeared to improve. This suggests that nonspecific exercise, such as walking, may have benefits on other muscle groups.[26] Handgrip strength may be another example, included here as a measure of overall muscular strength, endurance,[27] and frailty.[28] Although there were no specific weights or targeted hand exercises included in either intervention, grip strength appeared to improve over time. This improvement may reflect reduced frailty due to overall increased levels of physical activity.

Unlike previous studies,[7,10,15,29] we did not observe a significant increase in 6MWT postintervention. Given the majority of participants ($n = 11/14$) improved individually on the 6MWT, it is likely that the trialled interventions could still be beneficial for walking distance, but our study lacked sufficient power to capture this. It is worth noting that no significant deterioration was observed on 6MWT after Week 12—as might be expected from PAH control groups who received no active intervention.[10] The 6MWD at the end of study intervention at Week 12 for both the MDR (544 m) and ET (438 m) was still above the threshold of 400 m that is associated with reduced risk of hospitalization or PAH-associated death.[30]

Outcomes at Week 26 follow-up were comparable to those at Week 12, with no apparent changes over the observational study period. This suggests that any functional gains achieved such as those in handgrip, symptoms of PAH, depression, and anxiety were maintained over time, after completion of the study interventions (RHC and cMRI were not repeated at week 26 for logistical reasons). There were no changes in PAH-specific medication, or further exercise intervention, in any participants during this time; however, we did not collect data to quantify incidental physical activity levels at follow-up. We hypothesize that any retention of benefits after the intervention period may have been due to participant behavioral change, or persistent physiological benefit. Future studies could explore this in more detail.

The results of this preliminary study must be interpreted within the context of several limitations. The major limitation of this study was its small sample size, due to challenges with study recruitment. This limited study power and the ability to detect between-group differences. We therefore cannot conclusively comment on the efficacy of trialed interventions, their effect sizes, or make comparisons. Furthermore, the small sample size and early study termination amplified apparent differences between the two groups, with uneven group allocation, demographic variability and subsequent withdrawals from the intervention group. Notable missing data—particularly for invasive RHC outcomes—is another limitation that may have contributed to biased preliminary estimates of treatment effects.

Given this was an exploratory study, a broad suite of outcome measures was included. This was important for conducting a preliminary evaluation of novel interventions and informing future research; however, multiple comparisons are acknowledged as a subsequent limitation. When formal corrections were applied, preliminary main effects did not retain statistical significance due to limited power. These results should be interpreted with caution and require corroboration in future larger powered trials. Nonetheless, this study provides direction for future research and suggests a focus on cMRI hemodynamic outcomes of interest (SVI and RVEF), which were more acceptable to potential study participants, may be prudent.

CONCLUSION

This study provides preliminary evidence that completion of a 12-week, low-intensity outpatient program (MDR or ET) is safe, feasible, and well-accepted by participants. Though not formally powered, results of this study suggest that outpatient exercise interventions may be associated with improved hemodynamic function (mPAWP, SV, and SVI), QOL (PH symptoms, depression, and anxiety), and muscular strength (VC and handgrip strength) for people with PAH. Larger studies are needed to confirm these results and to explore the comparative efficacy and dose-responsiveness of these two interventions.

AUTHOR CONTRIBUTIONS

Karen S. W. Chia conceived the initial hypothesis, protocol, established the project, analyzed the data, and authored the paper. Christine T. Shiner assisted with protocol implementation, ethics requirements, analyzed the data, and critically reviewed the manuscript. Karen Brown assisted with ethics requirements, recruitment, study visits, protocol implementation, and manuscript review. Cameron J. Holloway and Camila Moreyra reviewed the protocol, provided cMRI expertise, reported all cMRIs and manuscript review. Nicole Bart, Peter K. K. Wong, Steven G. Faux assisted with protocol review, protocol implementation, manuscript review. Eugene Kotlyar assisted with recruitment, protocol development, protocol implementation, manuscript review and supervised the project. All authors have read and approved the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

Ethics approval was obtained from St Vincent's Hospital Human Research Ethics Committee (HREC/14/SVH/340). Australian and New Zealand Clinical Trials Registry: ACTRN12615001041549.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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